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     FILE 'USPATFULL' ENTERED AT 15:38:03 ON 05 JAN 2000
L1          4778 S GH OR (GROWTH ADJ HORMONE)
L2          1613 S L1 AND CRYSTAL?
L3        239323 S PH OR (NEUTRAL ADJ PH)
L4        239445 S METHANOL OR ETHANOL OR PROPANOL
L5           661 S L2 AND L3 AND L4
L6           261 S RECRYSTAL? AND L5
L7           138 S BUFFER AND L6
L8           542 S CRYSTAL? (3A) BUFFER

=> s l7 and l8

L9             0 L7 AND L8

=> s l6  and l8

L10            0 L6 AND L8

=> s l5 and l8

L11            4 L5 AND L8

=> d l11 1-4


L11  ANSWER 1 OF 4  USPATFULL
AN     1998:157309  USPATFULL
TI     Pharmaceutical formulation
IN     S.o slashed.rensen, Hans Holmegaard, Virum, Denmark
       Skriver, Lars, Ved.ae butted.k, Denmark
       Hoelgaard, Annie Rassing, Holte, Denmark
PA     Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI     US 5849704  19981215
AI     US 1995-458386  19950602 (8)
RLI    Continuation-in-part of Ser. No. US 1993-12817, filed on 3 Feb 1993
       which is a continuation-in-part of Ser. No. US 1992-827200, filed on 28
       Jan 1992
PRAI   DK 1991-2046        19911220
       DK 1992-1364        19921110
DT     Utility
LN.CNT 1071
INCL   INCLM: 514/012.000
       INCLS: 514/021.000; 530/362.000; 530/363.000; 530/397.000; 530/399.000
NCL    NCLM:  514/012.000
       NCLS:  514/021.000; 530/362.000; 530/363.000; 530/397.000; 530/399.000
IC     [6]
       ICM: A61K037-02
       ICS: A61K047-10; A61K047-26
EXF    514/12; 514/21; 530/399; 530/397; 530/362; 530/363
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11  ANSWER 2 OF 4  USPATFULL
AN     1998:157305  USPATFULL
TI     Pharmaceutical formulation
IN     S.o slashed.rensen, Hans Holmegaard, Virum, Denmark
       Skriver, Lars, Ved.ae butted.k, Denmark
       Hoelgaard, Annie Rassing, Holte, Denmark
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PA Novo Nordisk A/S, Bagsvaerd, Denmark (non-U.S. corporation)
PI US 5849700 19981215
AI US 1995-458385 19950602 (8)
RLI Continuation-in-part of Ser. No. US 1993-12817, filed on 3 Feb 1993, now
abandoned which is a continuation-in-part of Ser. No. US 1992-827200, filed on 28 Jan 1992, now abandoned
PRAI DK 1991-2046 19911220
DK 1992-1364 19921110
DT Utility
LN.CNT 1020
INCL INCLM: 514/012.000
INCLS: 514/021.000; 530/362.000; 530/363.000; 530/397.000; 530/399.000
NCL NCLM: 514/012.000
NCLS: 514/021.000; 530/362.000; 530/363.000; 530/397.000; 530/399.000
IC [6]
ICM: A61K038-18
ICS: A61K038-00; C07K014-61
EXF 514/12; 514/21; 530/399; 530/397; 530/362; 530/363
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 3 OF 4 USPATFULL
AN 1998:82875 USPATFULL
TI Growth hormone **crystals** and a process for production of growth hormone **crystals**
IN Junker, Flemming, Humleb.ae butted.k, Denmark
Theisen, Claus Friss, K.o slashed.benhavn, Denmark
PA Novo Nordisk A/S, BAgsvaerd, Denmark (non-U.S. corporation)
PI US 5780599 19980714
AI US 1994-350758 19941207 (8)
RLI Continuation of Ser. No. US 1994-222515, filed on 1 Apr 1994, now abandoned which is a continuation of Ser. No. US 1993-961932, filed on 13 Jan 1993, now abandoned
PRAI DK 1990-1687 19900713
DT Utility
LN.CNT 440
INCL INCLM: 530/399.000
INCLS: 530/420.000; 530/422.000; 530/304.000; 530/305.000
NCL NCLM: 530/399.000
NCLS: 530/304.000; 530/305.000; 530/420.000; 530/422.000
IC [6]
ICM: A61K038-27
EXF 530/399; 530/420; 530/422; 530/304; 530/305
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L11 ANSWER 4 OF 4 USPATFULL
AN 1998:34044 USPATFULL
TI Process for manufacturing **crystals** of growth hormone and **crystals** thereby obtained
IN Florin-Robertsson, Ebba, Stockholm, Sweden
Hokby, Elvy, Enskede, Sweden
Lundin, Ronny, Ekero, Sweden
Thome, Sirkka, Stockholm, Sweden
Westin-Sjodahl, Gertrud, Sodertalje, Sweden
PA Pharmacia & Upjohn Aktiebolag, Stockholm, Sweden (non-U.S. corporation)
PI US 5734026 19980331
WO 9410192 19940511
AI US 1995-424450 19950524 (8)
WO 1993-SE885 19931027
19950524 PCT 371 date
19950524 PCT 102(e) date
PRAI SE 1992-3175 19921028
SE 1993-2278 19930702
SE 1993-885 19931027
DT Utility

```
LN.CNT 624
INCL    INCLM: 530/424.000
        INCLS: 530/399.000; 530/418.000; 530/419.000; 530/422.000
NCL     NCLM:  530/424.000
        NCLS:  530/399.000; 530/418.000; 530/419.000; 530/422.000
IC      [6]
        ICM: C07K014-61
        ICS: C07K001-14; C07K001-30
EXF     530/350; 530/399; 530/418; 530/419; 530/422; 530/424; 514/2; 117/43;
        554/211
CAS INDEXING IS AVAILABLE FOR THIS PATENT.


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     (FILE 'HOME' ENTERED AT 15:37:32 ON 05 JAN 2000)

     FILE 'USPATFULL' ENTERED AT 15:38:03 ON 05 JAN 2000
L1          4778 S GH OR (GROWTH ADJ HORMONE)
L2          1613 S L1 AND CRYSTAL?
L3        239323 S PH OR (NEUTRAL ADJ PH)
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L7           138 S BUFFER AND L6
L8           542 S CRYSTAL? (3A) BUFFER
L9             0 S L7 AND L8
L10            0 S L6  AND L8
L11            4 S L5 AND L8

=> d l11 4 kwic


L11  ANSWER 4 OF 4  USPATFULL
TI     Process for manufacturing crystals of growth hormone and
     crystals thereby obtained
AB     A process for manufacturing crystals of growth hormone (
     GH) comprising the steps of:
AB     i) mixing GH with an aqueous solution comprising a buffer and
       a chemical compound with the general formula (1):
AB     iii) isolating the crystals is provided. The crystals
       are in the form of needles, trigonal forms, cubes or parallelepipeds
       with a length of at least 20 microns.
SUMM   The present invention relates to a process for manufacturing
     crystals of growth hormone (GH) or functional
       derivatives thereof. It also relates to crystals of growth
       hormone and compositions containing them.
SUMM   A different way to circumvent the stability and production problems of
     GH is presented in this patent application.
SUMM   By crystallization a new way of manufacturing growth hormone
       can be achieved.
SUMM   Crystals of growth hormone can also be used for various new
       formulations of the hormone like e.g. injectable suspensions, implants
       and. . .
SUMM   Crystallization of growth hormone has not previous been
       possible to perform in an industrial way.
SUMM   Clarkson et al reports in J Mol Biol (1989), 208, 719-721 of three
       distinct crystallization methods, different from the earlier
       described method.
SUMM   1. Hanging drop and using ethanol or methanol in the
       buffer in which tetragonal bipyramids were obtained with a size of
       10.sup.-3 mm.sup.3, and a cell dimension of. . .
SUMM   The authors commented that they did not succeed in obtaining large
       single crystals.
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SUMM In WO 92/00998, Novo Nordiska NS, a method of producing chemically stable and biological active growth hormone cation **crystals** are disclosed. The method comprises the steps: addition of cations to a solution of **GH** at a **pH** between 5 and 8, growing of **crystals** at a temperature of 0.degree.-30.degree. C. and isolation of the **crystal**. The **crystal** obtained is a cation **GH crystal**.

SUMM The obtained **crystals** always include a cation and are small. In the examples the length of the zinc containing **crystals** varies between 3 and 12 micron.

SUMM . . . demand is to provide either ready to use injection solutions or to provide an injectable depot formulation, e.g., as suspended **crystals** of hGH. **Crystals** of hGH can be used in a suspension or in an aqueous injectable solution together with buffers and with or. . . an oily or aqueous suspension or as an implant, and thus give a slow release of the medicament. If the **crystals** are large enough, the can be used as powder and be spread on the surface, e.g., on a wound. Very. . .

SUMM We have to our great surprise found a new method for producing pure, active **GH crystals** without the addition of cations or solvents such as **methanol**, **ethanol**, acetone or paraldehyde, which are not acceptable from a therapeutic viewpoint.

SUMM By this new method the **crystals** could be formed within a very short period of time. When using some of the named compounds, see example 22, the **crystals** were formed instantly and for some others within one hour. This can be compared with the method presented by Carlsson et al. which only produces **crystals** after several weeks. By the addition of a chemical compound with the general structure (I) to an aqueous solution of **GH**, **crystals** of **GH** can be easily and rapidly formed. The addition can preferably be performed in the last purification step by dialysis or. . .

SUMM With this method it is possible to vary the size of the **crystals** depending on the conditions and time, which is a great advantage when preparing different formulations for administration of hGH.

SUMM The obtained **GH** in **crystals** is a material normally containing over 80% monomeric **GH**.

SUMM It could be a great advantage in the manufacturing of hGH, that there is a quick method for preparing **crystals** and with avoidance of cations.

SUMM The new process for manufacturing **crystals** of growth hormone (**GH**) or functional derivatives thereof thus includes the steps:

SUMM i) mixing **GH** or functional derivatives thereof with an aqueous solution comprising a buffer and a chemical compound with the general formula (I):

SUMM iii) isolating the **crystals** by known methods.

DRWD The FIGURE is a microscopy of formed **crystals**.

DETD By incubation is meant all different types of **crystallization** processes known for a person skilled in the art.

DETD . . . scale the easiest way is by letting the solution stand. The compound is preferably chosen among benzyl alcohol, 2-methylbenzyl alcohol, 1-(1-naphthyl)**ethanol**, phenylethanol, 1-phenyl-1-**propanol**, 2-phenyl-2-**propanol**, and 3-phenyl-1-**propanol**.

DETD . . . invention is also related to the use of a chemical compound with the general formula (I) for the preparation of **crystals** of **GH** from a buffered solution.

DETD An initial **pH** of 5.8 to 6.3 and preferably 6.2 has given good results. The formation of **crystals** is depending on time, **pH** and temperature. At a temperature of between 20.degree. C. and 30.degree. C. the **crystals** are normally rapidly formed, sometimes instantly and mostly within an hour.

DETD Also disclosed are **crystals** of growth hormone or any

functional analogue thereof in the form of needles, trigonal forms, cubes or parallelepipeds with a length of at least 20 micron. In some cases the obtained **crystals** were even more than 1 mm. Preferably the length is at least 50 to 2000 micron and more preferably 100 to 300 micron. The disclosed **crystals** are thus bigger than the **crystals** earlier obtained.

DETD The disclosed **crystals** can be useful in human and veterinary usage for various administration form, e.g. topical, nasal, pulmonal, oral, rectal and parenteral.

DETD Suspensions for injection, depot formulation and dry formulation comprising **crystals** according to the invention are also disclosed.

DETD . . . need of growth hormone or any functional analogue thereof by administering the disclosed formulation as well as for use of **GH crystals** for the manufacturing of a medicament for treating a patient in need of growth hormone or any functional analogue thereof.

DETD The disclosed process can be used in a purification process for **GH**.

DETD The disclosed **crystals** have been shown to be biologically active.

DETD By growth hormone (**GH**) is meant both naturally occurring and recombinant **GH** (rGH). By functional analogues are meant compounds having the same therapeutic effect as the growth hormone in the animal. Preferred. . .

DETD By using **crystals** of **GH** the formulation is not dependent on its solubility in the used carried buffer which gives a limitation to the amount of **GH** per volume. This is a clear advantage of the disclosed **crystals**.

DETD In a dry composition, a suspension or a depot formulation the amount per volume of **GH** in the drug delivery system could be very high.

DETD Formed **crystals** are shown in the FIGURE: Microscopy of formed **crystals**

DETD The formation of needles in different solutions was followed in examples 1-20 and 22. The obtained hGH **crystals** were characterized.

DETD The **crystals** were centrifuged and the supernatant was taken away with a pipette. The residue was washed and centrifuged 6 times with water, thereafter 3 times with acetonitrile and finally twice with diethylether. The **crystals** were dried.

DETD AshaiPac-OD 550, reversed phase/TRIS (**pH** 8.5)--n-**propanol**, isocratic.

DETD Superdex 75/0.05M phosphate buffer **pH** 7.4.

DETD The appearance of the solutions were eye-inspected according to **Ph**. Eur. 2nd Ed.

DETD **pH**

DETD **pH** was measured with glass and calomel electrodes.

DETD . . . 1 1 1 1.25 1 1 1 1 1 Volume, ml 1 1 1 1 1 3.4 1 1 1 1

Starting values:

pH 6.3 6.3 6.2 6.2 6.1 6.2-6.3 6.2 6.2 6.2 6.2

visual inspect.

clear clear

clear
clear
clear
clear
clear
clear
clear
clear

The results after 3
weeks' storage at
30.degree. C.:
pH 6.3 6.3
-- -- -- 6.2 6.3
6.3
6.3
6.4

visual inspect.
clear
clear
cryst
cryst
cryst
cryst
cryst
cryst

. . . 1 1 1.5
1.5
1.5 -- -- -- --

Volume, ml
1 1 1 1 1 1 1 3 1 1

Starting values:
pH 6.2 6.2
6.2
6.2
6.2
6.1 6.3
6.3
6.1
6.3

visual inspect.
clear
clear
clear
op**
op**
op**
clear
clear
clear
clear

The results after 3
weeks' storage at
30.degree. C.:
pH 6.3 6.3
6.3 6.4
6.2
6.2
6.4

visual inspect.
cryst
cryst
cryst clear
clear
clear

clear

The result after 3 months' storage at 5.degree. C.

pH 6.3 6.3 6.3 6.3 6.3

visual inspect. cryst cryst cryst clear clear

---

*x means a mixture of 1 .7 mM Na. . .

DETD Normally our formulations comprising benzyl alcohol gave **crystals** in the **pH** range of 6.1 to 6.3 and the solutions without benzylalcohol gave no **crystals** within this **pH** range. Formulations 1 and 2 were clear in spite of the addition of benzyl alcohol at **pH** 6.3 which appears to be a critical value for the formation of **crystals** in benzyl alcohol.

DETD The **crystals** were in the form of needles of different length. The biggest were about 0.3.times.0.03 mm. See FIG. 1.

DETD The melting point was performed on a Leitz-Wetzlar microscope. No melting point could be observed. The **crystals** were intact up to 230.degree. C., when they started to be miscoloured. At about 290.degree. C. the **crystals** were black but not melted. (pyrolysis)

DETD The **crystals** were insoluble in organic solvents such as dichloromethane, acetonitrile, **ethanol**, dimethyl formamide, and diethylether. They were difficult to dissolve in water and 70% **ethanol** in water but soluble in acids such as 1% acetic acid, 6M HCl and in a base such as 0.1M phosphate buffer, **pH** 8.

DETD The **crystals**, dissolved in 10% acetic acid and the buffer components, i.e. citric acid, mannitol, glycine and benzylic alcohol were investigated.

DETD The **crystal** sample did not migrate in this system, whereas all buffer components did.

DETD The **crystal** sample absorbed UV-light and showed positive reaction with ninhydrin and permanganate reagents, indicating the presence of aromatic groups, amino groups. . .

DETD Hydrolysis in 6M HCl, 110.degree. C., 20 hours of the **crystal** sample and hGH reference. Analysis by using TLC showed identical spots.

DETD The **crystal** sample was almost identical with the hGH reference.

DETD Experimental data obtained on the **crystals** was in good agreement with the theoretical value as well as with the hGH reference sample. See table below:

DETD

Component	Theoretical value	**crystals**
Asp	20	19.9
Thr	10	9.7
Ser	18	17.8
Glu	27	26.8
Pro	8	8.2
Gly	8	8.2
Ala	7	7.0
Half-cys	4	3.2
Val	7	7.2
Met	3	3.0
IIe. . .		

DETD The protein content of the **crystal** sample, based on an amount of 0.22 mg, was 84%. The content in the reference material (0.45 mg) was

91%.

DETD No **crystals** were formed in a solution containing:

DETD at a **pH** of 6.4.

DETD With the addition of more benzyl alcohol (i.e. >1%) the **crystals** were however rapidly formed.

DETD **Crystals** were also produced by lowering **pH** closer to 6 or under 6.

DETD The morphology of the **crystals** could be varied by **pH** and growth rate. When **pH** is closer to 6.3 the **crystals** are like needles and parallelepipeds.

DETD Within 24 hours **crystals** are formed with a length of 0.1 to 0.3 mm and about 0.001 to 0.005 mm thick.

DETD By varying the **pH** the size of the **crystals** could thus be changed.

DETD Smaller **crystals** are formed within a shorter time.

DETD Other chemical compounds were investigated for the possibility of forming **crystals** of growth hormone.

DETD The method "hanging drop" was used for investigation of useful agents for **crystallization** of growth hormone. The "hanging drop" method is described in **Crystallisation** of Nucleic Acids and Proteins, A practical approach, by A Ducruix and R Giege, IRL Press at Oxford, 1991, pages. . .

DETD **pH** 6.2

DETD The results were the following with the different **crystallisations** agents:

DETD

Compound	**Crystals**
benzyl alcohol	large single
.+-.1-(1-naphthyl)**ethanol**	large single
(.+-.)phenylethanol	large single
+phenylethanol	large single
-phenylethanol	large single
1-phenyl-1-**propanol**	large single
(.+-.)1-phenyl--**propanol**	large single
2-phenyl-2-**propanol**	large single
3-phenyl-1-**propanol**	large single
2-methylbenzyl alcohol	single

DETD For some of the used **crystallization** agents the **crystals** were formed slower. When using .+-.1-(1-naphthyl) **ethanol** the **crystals** were formed after a couple of weeks, and the size was 200 to 500 microns. Instead of using Na-citrate, also. . .

DETD A higher concentration of the **crystallization** agent was, however, needed when no citrate was present.

DETD When other **crystallization** agents were tested in the same way as above, falling outside the general formula (I), no **crystals** were formed:

DETD

Compound	**Crystals**
3-methyl-4-nitrobenzyl alcohol	none
2-nitrobenzyl alcohol	none
4-nitrobenzyl alcohol	none
1-naphthol	none
2-naphthol	none
phenol	none

benzaldehyde none
benzylamine none
(-)1-phenyl-1-butanol none
L-phenylglycinol none

DETD Immunological analysis of the **crystals** was performed. The **crystals** were formed according to examples 1-20 in a buffer containing:

DETD 0.17 mg of the formed **crystals** were dissolved in 0.340 ml 0.05M phosphate buffered saline, **pH** 7.5 containing 0.05% Tween 20. The solution was further diluted in 10 fold steps in the same buffer. All individual. . .

DETD An enzyme-linked immunosorbent assay, ELISA, Immunosorbent assay, was used to measure rhGH in the dissolved **crystals**.

DETD **Crystals** have been grown from a solution according to example 6 above and dispensed as 0.5 ml samples in glass containers. After preparation the solution was stored at 25.degree. C. for 1 week for the **crystals** to grow. They were stored further at 5.degree. C. for 3 months prior to **crystal** harvesting. When the **crystals** were harvested the supernatant surrounding the **crystals** was sucked of. The **crystals** were rinsed twice with 0.25 ml of buffer according to example 6 (i.e. the composition according to example 6 except for the growth hormone). The second rinsing step was terminated by centrifugation of the **crystals** prior to discarding the rinsing **buffer**. The remaining **crystals** were dissolved in 0.5 ml of buffer of 5 mM sodium citrate, 12 mM glycine and 130 mM mannitol, **pH** 6.1. Several samples were pooled to be used in the bioassay analysis.

DETD . . . was run on a sample prepared according to the above procedure. The growth hormone showed to be 100% monomeric after **crystallization** and subsequent dissolution.

DETD Bioassay of Dissolved Growth Hormone (**GH**) **Crystals**

DETD To investigate whether the **GH crystals** obtained were biologically active, a weight gain assay in hypophysectomized rats was performed.

DETD . . . groups of 15. They were treated twice daily for 4 days with either an in-house standard preparation of human recombinant **GH** (calibrated against WHO 80/505 to have a biological potency of 4.5 IU/vial) or the solution made from **GH crystal** at two doses. Standard doses were 0.04 IU/day and 0.16 IU/ml.

DETD . . . injection (day 5) The difference between these weights were calculated and the potency determined by comparing the results of the **crystal** solution treated animals with those of the standard treated groups.

DETD

Dose	0.04 IU/day		0.16 IU/day	
Standard	12.2	8.9	17.7	8.7
GH crystals	17.3	8.0	21.3	1.7

DETD The biological potency of the dissolved **GH crystals** was found to be 7.1 IU/ml.

DETD Thus, we have demonstrated that the human growth hormone in dissolved **GH crystals** is biologically active in vivo.

CLM What is claimed is:

1. Process for manufacturing **crystals** of human growth hormone (**GH**) in the form of needles, trigonal forms, cubes or parallelepipeds with a length of at least 20 microns, which comprises the following steps: i) mixing human **GH** with an aqueous solution consisting essentially of a buffer and a chemical compound with the general formula (1): Ar--(--CR.sub.1 R.sub.2. . . 1, and in the

absence of added cations and in the absence of solvents selected from the group consisting of **methanol**, **ethanol** and paraldehyde; ii) incubating; and iii) isolating said **crystals** with a length of at least 20 microns; and wherein said solution has an initial **pH** of 5.8 to 6.3 and the concentration of said buffer is about 2 to about 50 mM.

2. Process according to claim 1, in which **GH** is recombinant human **GH** (rhGH).

. . . The process according to claim 1 wherein said compound is selected from the group consisting of benzyl alcohol, 2-methylbenzyl alcohol, 1-(1-naphthyl)**ethanol**, phenylethanol, 1-phenyl-1-**propanol**, 2-phenyl-2-**propanol**, and 3-phenyl-1-**propanol**.

6. Process according to claim 2 in which the compound is selected from the group consisting of benzylalcohol, 2-methylbenzylacohol, 1-(1-naphthyl)**ethanol**, phenylethanol, 1-phenyl-1-**propanol**, 2-phenyl-2-**propanol**, and 3-phenyl-1-**propanol**.

7. The process of claim 1 wherein the length of said **crystals** is 50 to 2000 microns.

8. The process of claim 1 wherein the length of said **crystals** is 100 to 300 microns.

15. The process of claim 1 wherein said **pH** is 6.2.

16. The process of claim 1 wherein said **pH** is 6.3.

18. The process of claim 17 wherein said **crystals** are formed within one hour.

. . . of at least 1%; said incubating is carried out at temperatures of between 20.degree. C. and 30.degree. C., and said **crystals** are formed within one hour.

. . . wherein said buffers includes a citrate and said compound is selected from the group consisting of benzyl alcohol, 2-methylbenzyl alcohol, 1-(1-naphthyl)**ethanol**, phenylethanol, 1-phenyl-1-**propanol**, 2-phenyl-2-**propanol**, 3-phenyl-1-**propanol**.

24. Process according to claim 19, in which **GH** is recombinant human **GH** (rhSH).

=> d l11 3 kwic

L11 ANSWER 3 OF 4 USPATFULL

TI Growth hormone **crystals** and a process for production of growth hormone **crystals**

AB A method of producing chemically stable and biologically active growth hormone **crystals** and processes for production of pharmaceutical preparations containing these growth hormone **crystals**.

SUMM The present invention concerns a method of producing growth hormone **crystals** in the presence of cations, novel growth hormone **crystals** and pharmaceutical preparations containing such novel **crystals**.

SUMM The growth hormones (**GH**) from man and from the common domestic animals are proteins of approximately 191 amino acids, synthesized and secreted from the. . .

SUMM . . . interest in the molecular function of this protein rests upon the commercial interests from both veterinarian and medical circles. The **GH** gene has now been cloned and human growth hormone (hGH) and Met-hGH are currently beeing produced biosynthetically by the use. . .

SUMM Pharmaceutical preparations of **GH** tend to be unstable. Degradation products such as deamidated or sulfoxydated products and dimer or polymer forms are generated--especially in solutions of **GH**. Therefore, today **GH** is lyophilized and stored in the lyophilized form at 4.degree. C. until it is reconstituted by the patient, before start. . .

SUMM . . . period of up to about 14 days. There is thus a need in the art for more stable preparations of **GH**.

SUMM It would also be an advantage to avoid the lyophilization step in the production of **GH** preparations. Lyophilization is a time consuming and costly process and also often a limiting procedure due to the capacity of. . .

SUMM The present invention is based on the surprising recognition that the above needs are fulfilled by means of a **crystallization** step in the production of **GH**.

SUMM Although readily available in quantities sufficient for **crystallization**, **GH** has so far eluded succesfull **crystallization**. Micro **crystals**, or amorphous material have been reported from a variety of sources: (Jones et al., Bio-Technology (1987) 5, 499-500; Wilhelmi et. . .

SUMM . . . in use for this purpose. Apparently due to heterogenicity among growth hormone preparations the size and the shape of the **crystals** have been reported to vary significantly. The largest **crystals** have been reported by Jones et al. (1987). For their successfull experiments they used a mixture of polyethylene glycol 3500 and beta octyl glucoside at neutral **pH**. Clarkson et al. (1989) reported that the use of lower alcohols and acetone permitted the generation of **crystals** of 0.001 to 0.005 cubic mm with varying shapes. None of the known methods are however suitable for commercial production of **GH crystals** a.o. due to the fact that growth times of from several weeks up to one year are needed.

SUMM . . . solutions were prepared in the presence of varying concentrations of denaturing solutes (1 to 4 M of urea) at high

pH (9.5). A reproduction of this process with hGH has shown that it is not possible to produce **crystals** in this way.

SUMM From the literature it is well known that the presence of divalent cations during the process of **crystallization** permits not only excellent orientation during analysis, but also improved physical conditions for the **crystallization** of insulin (e.g. U.S. Pat. No. 2,174,862). Growth hormone is, however, more than three times larger than insulin and has. . . totally different conformation. Surprisingly the addition of cations to solutions containing hGH have now permitted the generation of stable, uniform **crystals** of the growth hormone in high yields. Furthermore, the time used for the formation of high quality hGH **crystals** is relatively short.

SUMM In its broadest aspect the present invention is related to a process for production of cation **crystals** of **GH** or **GH** derivatives, comprising the following steps:

SUMM a) adding cations of inorganic or organic nature to a solution of **GH** or derivatives thereof at a **pH** between 5 and 8,

SUMM b) growing of **crystals** at a temperature from about 0 to about 30.degree. C., and

SUMM c) isolation of the cation **crystals** by known means.

SUMM In the present context **GH** is intended to cover all species of **GH** including human, bovine, porcine, ovine, salmon, trout or tuna. **GH** derivatives are intended to cover **GH** of human or animal species with minor variation in the protein sequence. Thus a few amino acid residues may have. . .

SUMM . . . process according to the present invention has for the first time made it possible to produce chemically stable and uniform cation-**GH crystals**. Also, the present process enables production of both larger and smaller **crystals** of growth hormone, as the need may be.

SUMM The **pH** in step a) is preferably from 5.0 to 7.5, more preferably from 5.0 to 6.8, even more preferably from 5.8. . .

SUMM . . . these an inorganic cation such as Zn.sup.++ has turned out to be well suited for the fast formation of stable **GH crystals**. Also mixtures of these cations can be used.

SUMM The cation should be added in an amount providing fast and efficient formation of well defined **crystals**. The upper limit for the amount of added cation is the amount which would cause unspecific precipitation of substantial amounts. . .

SUMM If Zn.sup.++ is used, suitable concentrations will typically be from about 0.2 to 10 mol Zn.sup.++ /mol **GH**. However, if the **crystallization** reaction mixture contains a buffer or other compound which is capable of binding some of the cation, e.g. in a. . . form, greater concentration of the cation will be needed because some of the cation will not be available for the **crystallization** process.

SUMM Zn.sup.++ will preferably be used in an amount which will cause formation of **GH crystals** with a molar ratio between Zn.sup.++ and **GH** from about 0.2 to about 10, preferably from about 0.5 to about 5 and more preferably from about 0.5 to. . .

SUMM . . . chosen from the group consisting of short chained aliphatic, cyclic or aromatic alcohols and ketones. Suitable organic solvents are acetone, **methanol**, **ethanol** and 2-**propanol**. A preferred organic solvent is **ethanol** or acetone. The concentration of the organic solvent may be from 0.1 to 50% v/v, preferably from 0.1 to 30%,. . .

SUMM . . . used as a fast and efficient down stream processing of the growth hormone in question, due to the formation of **crystals** in large volumes of solutions.

SUMM The present invention is also related to novel cationic **crystals** of **GH** or **GH** derivatives.

SUMM The **crystals** are preferably hGH **crystals** or

crystals of derivatives of hGH. The cation is preferably Zn.sup.++ and the molar ration between Zn.sup.++ and **GH** will typically be from about 0.2 to 10, preferably from 0.5 to 5 and more preferably from 0.5 to 2.0. The size of the **crystals** will be dependent on the Zn.sup.++ to **GH** ratio and the choice and content of solvent used in the process. hGH **crystals** according to the present invention have been shown to have a biological potency similar to that of a solubilized hGH standard in in vitro and in vivo tests. The novel **GH crystals** can thus be used for the same indications as the commercially available hGH preparation.

SUMM Pharmaceutical preparations containing the novel **GH crystals** will typically be solutions or suspensions and may contain the usual adjuvants and additives used for pharmaceutical hGH preparations, such. . . as buffers, glycerol and preservatives. The preparations may be administered in the same way as the commercial hGH preparations. The **crystals** may also be formulated as dried **crystals** which will then have to be reconstituted before start of use.

SUMM The pharmaceutical preparations containing the novel **GH crystals** have surprisingly a very high chemical stability compared with preparations made from commercially available **GH** .

SUMM . . . of production of pharmaceutical preparations that are more convenient, especially for the patients. Due to the high stability of the **crystals** in suspension, the present invention will as an example make it possible to produce ready to use pharmaceutical preparations in. . .

SUMM In a further aspect the invention provides a valuable tool for production and purification purposes of **GH**.

DRWD FIG. 1 is a photomicrograph of human growth hormone **crystals** formed by the method of the invention.

DETD . . . than about 0.1 mg/ml, more preferably from about 4 to about 7 mg/ml and most preferred about 6 mg/ml. The **pH** will preferably be from 6.0 to 6.3.

DETD To the above mentioned solution may be added an organic solvent. A preferred organic solvent is **ethanol** in a concentration which may vary between 0.1 and 20%, preferably 5 and 15%, and most preferred 6 and 12%.

DETD Other solvents such as acetone, **methanol** or **propanol** may be used alone or as a mixture instead of or together with **ethanol** in a concentration within the range of from 1 to 50%.

DETD A preferred cation is Zn.sup.++ which will normally be used in a concentration from 0.5 to 10 mol/mol **GH**, preferably from 1.0 to 3.0 mol/mol **GH**, more preferred from 1.1 to 2.2 mol/mol **GH** and most preferred from 1.2 to 2.0 mol/mol **GH**.

DETD If cations of inorganic nature other than Zn.sup.++ are used, the concentration may be varied between 0.5 and 10 mol/mol **GH**.

DETD The **crystals** are then grown for a period of from 1 to 120 hrs. preferably 5-72 hrs., most preferred 20-48 hrs., and. . .

DETD The **crystals** may be recovered by centrifugation or filtration, followed by washing and/or freeze drying to remove remaining organic solvents.

DETD Pharmaceutical preparations of dried **crystals** or **crystals** in suspension can now be formulated by using various selected buffers and other pharmaceutically acceptable additives.

DETD **Crystallization** of hGH in the presence of Zn.sup.++.

DETD . . . 5, 161-164, in a concentration of 6 mg/ml was incubated in 10 mM phosphat buffer (NaH.sub.2 PO.sub.4) and adjusted to **pH** 6.1 with H.sub.3 PO.sub.4. Acetone was added to a final concentration of 10% (v/v) and thereafter zinc acetate solution was. . .

DETD The resulting solution was left at 15.degree. C. for 20 hours, whereby **crystals** were allowed to form.

DETD After this the **crystals** were recovered and washed 3 times with

crystallization buffer without acetone. The **crystallization** was checked by microscopy and the size of the **crystals** were measured to 8-12 .mu.m. A photomicrograph is shown in FIG. 1.

DETD The **crystal** yield of hGH was determined by solubilization of the washed **crystals** in 7M urea followed by ion exchange HPLC analysis.

DETD Example 1 was repeated with the exception that Met-hGH was used instead of hGH. The **crystals** recovered by this process were identical in shape and size to those obtained with hGH. The yield was more than. . .

DETD The **crystals** of hGH resulting from this procedure were much smaller than the **crystals** resulting from Example 1, less than 2 .mu.m.

DETD Example 1 was repeated under conditions where acetone was exchanged with **ethanol** and temperature during growing period was 20.degree. C. instead of 15.degree. C. All other experimental conditions were identical to those described in example 1. By varying the **ethanol** concentration the optimal concentration was found to be 7.5% (v/v). The yield was increased to >80% if the motherfluid following initial **crystallization** for 16 hrs was supplemented with further 4% (v/v) **ethanol** and the **crystallization** temperature was lowered from 20.degree. to 10.degree. C. over a period of 16 hrs. The size of the **crystals** were between 3 to 6 .mu.m with a shape similar to that described in example 1.

DETD Determination of the amount of Zn bound in hGH **crystals**

DETD Example 1 was repeated with the exception that **ethanol** in a concentration of 7.5% (v/v) was added instead of acetone and that **crystals** were allowed to form for 16 hrs at 20.degree. C., then the **crystals** were separated from the motherfluid by centrifugation and washed once with 10 mM phosphate **buffer**. The **crystals** were solubilized by raising the **pH** to 8.0 with NaOH. The hGH was measured by ion exchange HPLC or by UV determination. The Zn concentration was measured by atomic absorption and the results were compared with those values obtained for the total **crystal** suspension. The ratio of bound Zn to hGH was found to be 1.9 mole of Zn per mole of hGH.

DETD **Crystals** were grown as described in example 5 and stored at 4.degree. C. The **crystals** were then isolated by centrifugation and subsequent removal of the motherfluid. Then the **crystals** were freeze dried over night to achieve dry **crystals** with no remaining organic solvent. A pharmaceutical suspension of the dried **crystals** was prepared according to the following formulation:

DETD

hGH **crystals**	1.3 mg/ml
NaH.sub.2 PO.sub.4, 2H.sub.2 O	3.0 mg/ml
Zn(Ac).sub.2, H.sub.2 O	0.1 mg/ml
Glycerol	15.0 mg/ml
Benzyl alcohol	15.0 mg/ml

DETD **pH** was adjusted to 6.2.

DETD

hGH **crystals**	1.3 mg/ml
NaH.sub.2 PO.sub.4, 2H.sub.2 O	3.0 mg/ml
Glycerol	15.0 mg/ml
Benzyl alcohol	15.0 mg/ml

DETD **pH** was adjusted to 6.2.

DETD The **crystals** were treated in the same way as in example 6 and the following suspension was formulated:

DETD

hGH **crystals**	1.3 mg/ml
NaH.sub.2 PO.sub.4, 2H.sub.2 O	2.5 mg/ml
NaCl	5.7 mg/ml
Benzyl alcohol	15.0 mg/ml

DETD **pH** was adjusted to 6.2.

DETD The **crystals** were treated in the same way as in example 6 and the following solution was prepared:

DETD

hGH **crystals**	1.3 mg/ml
NaH.sub.2 PO.sub.4, 2H.sub.2 O	2.14 mg/ml
NaCl	9.0 mg/ml

DETD **pH** was adjusted to 6.1.

DETD To estimate the in vivo biological potency of the hGH **crystals** prepared according to the invention a tibia test was performed using hypophysectomized rats. The test was performed in accordance with. . .

DETD Two preparations of hGH **crystals** produced according to example 1 and formulated as preparations according to exampel 9 (F-7 and F-8) each containing an estimated. . .

DETD From the performed test it can be concluded that the hGH **crystals** according to the invention are equally biological potent as the solubilized hGH standard and therefore will have a bioavailability equal. . .

DETD hGH **crystals** were grown as described in example 5. Immediately before use a suspension was prepared by centrifugation of the **crystals**, subsequent removal of the motherfluid, and resuspension of the **crystals** in sterile 10 mM NaH.sub.2 PO.sub.4, **pH** 6.2 giving a final concentration of 0.16 mg hGH/ml suspension.

DETD The suspension was used to estimate the potency of the hGH **crystal** preparation in a weight gain assay. The test was performed in accordance with the method described in the European Pharmacopoeia,. . .

DETD Two preparations of hGH **crystals** were used, each containing the same amount of hGH protein as the preparations of a growth hormone standard, which they. . .

DETD The potency of the hGH **crystal** preparations were found to be 92.6% of the standard. The 95% confidence limits were 79.1-126.4% of the standard.

DETD The hGH **crystal** preparation was thus shown to have a biological potency equal to that of the solubilized hGH standard.

DETD Stability of hGH **crystals** stored in suspension for 6 months at 22.degree.-24.degree. C.

DETD The **crystals** were formed as described in Example 1 with the exception that 7.5% (v/v) acetone was added instead of 10%.

DETD The **crystals** were allowed to remain in suspension in the mother fluid for 6 months at 22.degree.-24.degree. C. A sample of hGH **crystals** were removed by centrifugation, washed once with **crystallization buffer** without acetone and solubilized by raising the **pH** to 8.0.

DETD The solublized hGH **crystals** were subjected to analysis on ion exchange HPLC and GPC for detection of desamido and split forms or dimers and. . .

DETD . . . hGH preparation stored at 25.degree. C. for 32 days the content of the main peak of hGH in reconstituted hGH **crystals** was superior to reconstituted lyophilized hGH, stored under comparable conditions (see table 2).

DETD TABLE 2

	Reconstituted hGH	**Crystals**
Storage	25.degree. C. 32 days	22-24.degree. C. 6 months
Main peak on IE-HPLC (%)	71.2	92.3
Dimer (%)	0.7	1.2
Polyiner (%)	0.3	0.3
Desamido (%). . .		

CLM What is claimed is:

1. A process for production of divalent cation **crystals** of growth hormone (**GH**) or derivative thereof, comprising the following steps: a) adding to a solution of growth hormone (**GH**) or derivative thereof, divalent inorganic cations and organic solvents or a mixture of organic solvents at a **pH** between 5.8 and 6.5 to obtain **crystals** of **GH**, b) growing of **crystals** of step (a) at a temperature from about 0.degree. C. to about 30.degree. C., and c) isolating said **crystals** grown at step (b).

3. A process according to claim 1, wherein the organic solvent is selected from the group consisting of acetone, **methanol**, **ethanol** and 2-**propanol**.

4. A process according to claim 1, wherein the organic solvent is **ethanol** or acetone.

11. A process according to claim 1, wherein the **pH** in step (a) is from 6.0 to 6.5.

18. Divalent cation **crystals** of human growth hormone (hGH) or derivative thereof prepared according to the process of claim 1.

19. **Crystals** according to claim 18, wherein the divalent cation is Zn.sup.++.

20. **Crystals** according to claim 18, wherein the molar ratio between Zn.sup.++ and hGH is from about 0.2 to about 10.

21. **Crystals** according to claim 18, wherein the molar ratio between Zn.sup.++ and (hGH) is from 0.5 to 5.

22. **Crystals** according to claim 18, wherein the molar ratio between Zn.sup.++ and (hGH) is from about 0.5 to 2.0.

23. A pharmaceutical preparation comprising the **crystals** of claim 18 and a pharmaceutically acceptable additive.

=> d l4 2 kwic

YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

1 ANSWERS ARE AVAILABLE. SPECIFIED ANSWER NUMBER EXCEEDS ANSWER SET SIZE
The answer numbers requested are not in the answer set.
ENTER ANSWER NUMBER OR RANGE (1):end

=> d l14 2 kwic

YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

L14 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2000 ACS
TI Oral **GLP**-1 formulations for antidiabetic and other therapeutic applications
IN **Hoffmann, James Arthur**
AB Methods and formulations are presented that provide for (a) the oral absorption of **GLP**-1 peptides that bind surfactants; and (b) long-term storage of formulations contg. these peptides. For example, a **GLP**-1/DSS complex is administered orally instead of parenterally, which is much more convenient for, and facilitates compliance with diabetic patients and persons with other **GLP**-1 treated conditions.
IT Metabolic diseases
(catabolic diseases; oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT Genes (animal)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**glp**-1, peptide product; oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT Peptides, biological studies
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PEP (Physical, engineering or chemical process); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(glucose-lowering peptide 1; oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT Antidiabetic agents
Antiobesity agents
Cardioprotectants
Myocardial infarction
Oral drug delivery systems
Preservatives
Protein sequences
Stroke
Surfactants
(oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT 106612-94-6 107444-51-9
RL: BAC (Biological activity or effector, except adverse); PEP (Physical,

engineering or chemical process); PRP (Properties); THU (Therapeutic use);
BIOL (Biological study); PROC (Process); USES (Uses)
(amino acid sequence; oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT 56-81-5, Glycerol, biological studies 99-76-3, Methylparaben 100-51-6,
Benzyl alcohol, biological studies 123-03-5, Cetylpyridinium chloride 128-49-4, Docusate calcium 145-42-6, Sodium taurocholate 151-21-3,
Sodium dodecyl sulfate, biological studies 302-95-4, Sodium deoxycholate
361-09-1, Sodium cholate 577-11-7, Docusate sodium 863-57-0, Sodium glycocholate 1984-06-1, Sodium caprylate 7491-09-0, Docusate potassium
7647-14-5, Sodium chloride, biological studies 9002-92-0, Brij 35
9002-93-1, Triton X-100 9005-65-6, Tween 80 9005-66-7, Tween 40
29777-99-9D, N-alkyl derivs. 59122-55-3, Dodecyl .beta.-D-glucopyranoside 75621-03-3
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical
process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)
IT 108-39-4, biological studies 108-95-2, Phenol, biological studies
RL: MOA (Modifier or additive use); PEP (Physical, engineering or chemical
process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(preservative; oral **GLP**-1 formulations for antidiabetic and other therapeutic applications)

=> d l14 3 kwic

YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS
IN Galloway, John Allison; **Hoffmann, James Arthur**
AB The present invention provides novel complexes consisting of certain glucagon-like peptide 1 (**GLP**-1) mols.,

R1XGluGlyThrSerAspValSerSerTyrLeuYGlyGlnAlaAlaLysZPheIleAlaTrpLeuValLysGly ArgR2 (R1=L-His, D-His, desamino-His, etc.; X=Ala, Gly, Val, etc.; Y,Z=Glu, Gln, Ala, etc.; R2=NH2, Gly-OH; pI=6.0-9.0) assocd. with a divalent metal cation that is capable of copptg. with a **GLP**-1 mol. Pharmaceutical compns. and methods of using such complexes for enhancing the expression of insulin in B-type islet cells is. . .

=> d l14 4 kwic

YOU HAVE REQUESTED DATA FROM FILE 'CAPLUS' - CONTINUE? (Y)/N:y

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2000 ACS
IN Galloway, John Allison; **Hoffmann, James Arthur**
AB Complexes of glucagon-like peptide 1 (**GLP**-1) and derivs. having .gtoreq.1 His residue and isoelec. points of 6.0-9.0 with divalent metal cations were prepd. for enhancing the expression of insulin in B-type

islet cells and for treating maturity onset diabetes mellitus. Thus, **GLP**-1 (7-36) amide (I) in HEPES buffer was treated with ZnCl2 in HEPES buffer followed by storage at ambient temp. for. . .

Medline CAPLUS Biosis Embase X

L17 0 GLP ADJ CRYSTAL

=> s glp and crystal

L18 3 GLP AND CRYSTAL

=> d l18 1-3

L18 ANSWER 1 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1999:404857 CAPLUS
DN 131:49498
TI Glucagon-like peptide-1 crystals
IN Hoffmann, James Arthur; Hermeling, Ronald Norbert; Narasimhan, Chakravarthy
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9930731	A1	19990624	WO 1998-US26480	19981214
W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 926159	A2	19990630	EP 1998-310245	19981214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
AU 9918218	A1	19990705	AU 1999-18218	19981214

PRAI US 1997-69728 19971216
US 1997-PV69728 19971216
WO 1998-US26480 19981214

L18 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1988:541262 CAPLUS
DN 109:141262
TI Phosphorus-31 spectral spin diffusion in crystalline solids
AU Kubo, Atsushi; McDowell, Charles A.
CS Dep. Chem., Univ. British Columbia, Vancouver, BC, V6T 1Y6, Can.
SO J. Chem. Phys. (1988), 89(1), 63-70
CODEN: JCPSA6; ISSN: 0021-9606
DT Journal
LA English

L18 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
AN 1978:518223 CAPLUS
DN 89:118223
TI Comparison of rheological studies on adsorbed emulsifier films with x-ray studies of the bulk solutions
AU Boyd, J. V.; Krog, N.; Sherman, P.
CS Queen Elizabeth Coll., Univ. London, London, Engl.

SO Theory Pract. Emulsion Technol., Proc. Symp. (1976), Meeting Date 1974, 123-33. Editor(s): Smith, Alec L. Publisher: Academic, London, Engl. CODEN: 38LIA8
DT Conference
LA English

L18 ANSWER 2 OF 3 CAPLUS COPYRIGHT 2000 ACS

AB . . . using different methods. The angular dependences of TSD for 31P spectral spin diffusion in single crystals of dipotassium .alpha.-D-glucopyranose-1-phosphate dihydrate (**GLP**) and triphenylphosphine (TPP) were detd. The 31P spin diffusion under the influence of extraneous protons is well described by a. . .

ST phosphorus 31 spin diffusion **crystal**; potassium glucopyranose phosphate hydrate spin diffusion; triphenylphosphine phosphorus 31 spin diffusion

L18 ANSWER 3 OF 3 CAPLUS COPYRIGHT 2000 ACS
AB . . . examd.: aq. solns. of mixts. of Span 20 and Tween 20, of glyceryl
monolinoleate (Dimodan LS), and of glyceryl lactopalmitate (**GLP**
). The rheol. properties of A 1:3 mol.rato of Tween 20:Span 20 and
Dimodan LS formed liq. cryst. phases in water and showed viscoelasticity
at the oil-water interface. Glyceryl lactopalmitate gave no liq.
crystal formation in water and the film adsorbed at an oil-water
interface exhibited only slightly non-Newtonian characteristics after
aging. Both the. . .
ST emulsifier adsorbed rheol soln diffraction; x ray diffraction emulsifier
soln; viscoelasticity emulsifier; liq **crystal** emulsifier

X

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    FILE 'USPATFULL' ENTERED AT 09:44:12 ON 05 JAN 2000
L19             0 S GLP (3A)  CRYSTAL?
L20            87 S GLP AND  CRYSTAL?
L21             0 S L20 AND TETRAGONAL
L22         45091 S PLATE (3A)LIKE
L23             0 S L19 AND L22
L24             0 S L20 AND L22
L25        103271 S FLAT AND ROD
L26             4 S L20 AND L25
L27             0 S  L20 AND L22

=> d l26 1-4


L26  ANSWER 1 OF 4  USPATFULL
AN      1999:24322  USPATFULL
TI      Newtonian drift control agent processes
IN      Hazen, James Lyle, Plainsboro, NJ, United States
PA      Rhodia Inc., Cranbury, NJ, United States (U.S. corporation)
PI      US 5874096  19990223
AI      US 1996-704430  19960826 (8)
RLI     Continuation of Ser. No. US 1994-177051, filed on 3 Jan 1994, now
        patented, Pat. No. US 5550224, issued on 27 Aug 1996
DT      Utility
LN.CNT 823
INCL    INCLM: 424/405.000
        INCLS: 424/406.000; 424/496.000; 424/500.000; 536/114.000; 514/777.000;
               514/782.000
NCL     NCLM:  424/405.000
        NCLS:  424/406.000; 424/496.000; 424/500.000; 514/777.000; 514/782.000;
               536/114.000
IC      [6]
        ICM: A01N025-02
EXF     424/405; 424/496; 424/500; 424/406; 536/114; 574/777; 574/782
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L26  ANSWER 2 OF 4  USPATFULL
AN      1998:128381  USPATFULL
TI      Guar as a deposition and bioefficacy aid
IN      Hazen, James Lyle, Plainsboro, NJ, United States
PA      Rhone-Poulenc Inc., Cranbury, NJ, United States (U.S. corporation)
PI      US 5824797  19981020
AI      US 1995-494481  19950626 (8)
RLI     Continuation-in-part of Ser. No. US 1994-177051, filed on 3 Jan 1994,
        now patented, Pat. No. US 5550224
DT      Utility
LN.CNT 1141
INCL    INCLM: 536/114.000
        INCLS: 536/123.000; 536/123.100; 514/054.000
NCL     NCLM:  536/114.000
        NCLS:  536/123.000; 536/123.100
IC      [6]
        ICM: C08B037-00
        ICS: C07H001-00; A01N043-04; A61K031-715
EXF     536/114; 536/123; 536/123.1; 514/54
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
```

L26 ANSWER 3 OF 4 USPATFULL
AN 1998:1466 USPATFULL
TI Newtonian drift control agents
IN Hazen, James Lyle, Plainsboro, NJ, United States
PA Rhone-Poulenc Inc., Cranbury, NJ, United States (U.S. corporation)
PI US 5705173 19980106
AI US 1996-704431 19960826 (8)
DT Utility
LN.CNT 832
INCL INCLM: 424/405.000
INCLS: 424/496.000; 424/500.000; 514/777.000
NCL NCLM: 424/405.000
NCLS: 424/496.000; 424/500.000; 514/777.000
IC [6]
ICM: A01N025-02
EXF 424/405; 424/496; 424/500; 536/114; 514/777; 514/782
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L26 ANSWER 4 OF 4 USPATFULL
AN 96:77875 USPATFULL
TI Guar as a drift control agent
IN Hazen, James L., One Red Oak Dr., Plainsboro, NJ, United States 08536
PI US 5550224 19960827
AI US 1994-177051 19940103 (8)
DT Utility
LN.CNT 794
INCL INCLM: 536/114.000
INCLS: 536/123.100; 536/124.000
NCL NCLM: 536/114.000
NCLS: 536/123.100; 536/124.000
IC [6]
ICM: C08B037-00
ICS: C07H001-00; A61K031-715; A01N043-04
EXF 536/114; 536/123.1; 536/124; 514/54
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d l26 1-4 ab

L26 ANSWER 1 OF 4 USPATFULL
AB Aerial spray or discharge drift is controlled in aqueous compositions via the use of selected non-visco-elastic amounts of guar, one or more derivatives of guar, or combinations thereof.

L26 ANSWER 2 OF 4 USPATFULL
AB Aerial spray or discharge drift is reduced, deposition improved and bioefficacy enhanced in aqueous compositions via the use of selected non-visco-elastic amounts of guar, one or more derivatives of guar or combinations thereof.

L26 ANSWER 3 OF 4 USPATFULL
AB Aerial spray or discharge drift is controlled in aqueous compositions via the use of selected non-visco-elastic amounts of guar, one or more derivatives of guar, or combinations thereof.

L26 ANSWER 4 OF 4 USPATFULL
AB Aerial spray or discharge drift is controlled in aqueous compositions via the use of selected non-visco-elastic amounts of guar, one or more derivatives of guar or combinations thereof.

=> d l26 4 kwic

L26 ANSWER 4 OF 4 USPATFULL
DETD . . . to bind free water, it is used to stabilize foods such as ice cream by inhibiting the formation of ice **crystals**. Guar is also utilized to stabilize certain delicate, non-food emulsions such as 1:1 mixtures of water and mineral oil.
DETD . . . range) were sufficient to cover the droplet spectra produced by the equipment and processing conditions used in our study, i.e., **flat** fan agricultural-type nozzles atomizing conventional agricultive formulations at normal pressures. The methodology conformed to **GLP** standards.
DETD . . . added from a twenty (20) milliliter syringe into the same area. Both were stirred briefly by hand with a stirring **rod**.

(All Search

:36 ON 05 JAN 2000)

FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 09:26:45 ON 05 JAN 2000

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                E HERMELING RONOLD/ AU
L1            4 S E1
L2            1 S E2
L3            0 S L1 AND GLP
L4            1 S L2 AND GLP
                E HOFFMANN JAMES A/AU
L5            2 S E2
L6           32 S E3
L7            1 S E4
L8           10 S E5
L9            4 S E5 AND GLP
L10           0 S E6 AND GLP
L11           0 S L5 AND GLP
L12           2 S L6 AND GLP
L13           0 S L7 AND GLP
L14           4 S L8 AND GLP

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L12  ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2000 ACS
AN   1998:682139  CAPLUS
DN   129:276356
TI   Glucagon-like peptide-1 analogs
IN   Hoffmann, James A.
PA   Eli Lilly and Co., USA
SO   PCT Int. Appl., 26 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
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PI   WO 9843658          A1   19981008      WO 1998-US5945   19980325
         W:  AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GE, GH,
             GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
             LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RU, SD, SG, SI, SK,
             SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG,
             KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA,
             GN, ML, MR, NE, SN, TD, TG
     AU 9865862          A1   19981022      AU 1998-65862    19980325
PRAI US 1997-41167     19970331
     WO 1998-US5945    19980325
OS   MARPAT 129:276356

L12  ANSWER 2 OF 2  CAPLUS  COPYRIGHT 2000 ACS
AN   1998:41714  CAPLUS
DN   128:111161
TI   Glucagon-like insulinotropic peptides, compositions and methods
IN   Galloway, John A.; Hoffmann, James A.
PA   Eli Lilly and Company, USA
SO   U.S., 8 pp. Cont.-in-part of U.S. Ser. No. 164,277, abandoned.
     CODEN: USXXAM
DT   Patent
LA   English
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FAN.CNT 3

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5705483	A	19980106	US 1995-407831	19950321
	CA 2137206	AA	19950610	CA 1994-2137206	19941202
	JP 07196695	A2	19950801	JP 1994-303404	19941207
	ZA 9504141	A	19961122	ZA 1995-4141	19950522
	NO 9502034	A	19960923	NO 1995-2034	19950523
	EP 733644	A1	19960925	EP 1995-303423	19950523
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
	HU 74729	A2	19970228	HU 1995-1508	19950523
	CA 2150080	AA	19960922	CA 1995-2150080	19950524
	FI 9502536	A	19960922	FI 1995-2536	19950524
	AU 9520268	A1	19961003	AU 1995-20268	19950524
	AU 708159	B2	19990729		
	CN 1131674	A	19960925	CN 1995-105569	19950526
	JP 08269097	A2	19961015	JP 1995-127910	19950526
	BR 9503036	A	19970923	BR 1995-3036	19950630
	US 5977071	A	19991102	US 1997-927227	19970910
PRAI	US 1993-164277	19931209			
	US 1995-407831	19950321			
OS	MARPAT 128:111161				

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L14 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2000 ACS
AN 1999:404857 CAPLUS
DN 131:49498
TI Glucagon-like peptide-1 crystals
IN **Hoffmann, James Arthur**; Hermeling, Ronald Norbert; Narasimhan, Chakravarthy
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9930731	A1	19990624	WO 1998-US26480	19981214
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 926159	A2	19990630	EP 1998-310245	19981214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 9918218	A1	19990705	AU 1999-18218	19981214
PRAI	US 1997-69728	19971216			
	US 1997-PV69728	19971216			
	WO 1998-US26480	19981214			

L14 ANSWER 2 OF 4 CAPLUS COPYRIGHT 2000 ACS
AN 1999:390390 CAPLUS
DN 131:49468
TI Oral **GLP**-1 formulations for antidiabetic and other therapeutic applications
IN **Hoffmann, James Arthur**
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 26 pp.

CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI WO 9929336	A1	19990617	WO 1998-US25515	19981202

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

	AU 9916173	A1	19990628	AU 1999-16173	19981202
PRAI	US 1997-67600	19971205			
	US 1997-PV67600	19971205			
	WO 1998-US25515	19981202			

L14 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2000 ACS
AN 1996:630467 CAPLUS
DN 125:266590
TI Glucagon-like insulinotropic complexes, pharmaceutical compositions containing them and their use for treating diabetes
IN Galloway, John Allison; **Hoffmann, James Arthur**
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 13 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 733644	A1	19960925	EP 1995-303423	19950523

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

	US 5705483	A	19980106	US 1995-407831	19950321
PRAI	US 1995-407831	19950321			
	US 1993-164277	19931209			
OS	MARPAT 125:266590				

L14 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2000 ACS
AN 1995:907629 CAPLUS
DN 124:30421
TI Preparation of complexes of glucagon-like peptide 1 with divalent metal cations.
IN Galloway, John Allison; **Hoffmann, James Arthur**
PA Lilly, Eli, and Co., USA
SO Eur. Pat. Appl., 10 pp.
CODEN: EPXXDW
DT Patent
LA English
FAN.CNT 3

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI EP 658568	A1	19950621	EP 1994-308950	19941202

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE

	CA 2137206	AA	19950610	CA 1994-2137206	19941202
	JP 07196695	A2	19950801	JP 1994-303404	19941207
PRAI	US 1993-164277	19931209			

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L4   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2000 ACS
AN   1999:404857  CAPLUS
DN   131:49498
TI   Glucagon-like peptide-1 crystals
IN   Hoffmann, James Arthur; Hermeling, Ronald Norbert; Narasimhan,
     Chakravarthy
PA   Eli Lilly and Company, USA
SO   PCT Int. Appl., 45 pp.
     CODEN: PIXXD2
DT   Patent
LA   English
FAN.CNT 1
     PATENT NO.         KIND  DATE          APPLICATION NO.  DATE
     ---------------    ----  --------      ---------------  --------
PI   WO 9930731          A1   19990624      WO 1998-US26480  19981214
         W:  AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE,
             GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK,
             LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD,
             SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM,
             AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA,
             GN, GW, ML, MR, NE, SN, TD, TG
     EP 926159           A2   19990630      EP 1998-310245   19981214
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, SI, LT, LV, FI, RO
     AU 9918218          A1   19990705      AU 1999-18218    19981214
PRAI US 1997-69728     19971216
     US 1997-PV69728   19971216
     WO 1998-US26480   19981214


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     (FILE 'HOME' ENTERED AT 09:26:36 ON 05 JAN 2000)

     FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 09:26:45 ON 05 JAN 2000
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L1             4 S E1
L2             1 S E2
L3             0 S L1 AND GLP
L4             1 S L2 AND GLP
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L16 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2000 ACS
AN 1999:404857 CAPLUS
DN 131:49498
TI Glucagon-like peptide-1 crystals
IN Hoffmann, James Arthur; Hermeling, Ronald Norbert; **Narasimhan, Chakravarthy**
PA Eli Lilly and Company, USA
SO PCT Int. Appl., 45 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9930731	A1	19990624	WO 1998-US26480	19981214
	W: AL, AM, AU, AZ, BA, BB, BG, BR, BY, CA, CN, CU, CZ, EE, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, RO, RU, SD, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	EP 926159	A2	19990630	EP 1998-310245	19981214
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
	AU 9918218	A1	19990705	AU 1999-18218	19981214
PRAI	US 1997-69728		19971216		
	US 1997-PV69728		19971216		
	WO 1998-US26480		19981214		

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FILE 'MEDLINE, CAPLUS, BIOSIS, EMBASE' ENTERED AT 09:26:45 ON 05 JAN 2000

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L2	1	S	E2
L3	0	S	L1 AND GLP
L4	1	S	L2 AND GLP
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L5	2	S	E2
L6	32	S	E3
L7	1	S	E4
L8	10	S	E5
L9	4	S	E5 AND GLP
L10	0	S	E6 AND GLP
L11	0	S	L5 AND GLP
L12	2	S	L6 AND GLP
L13	0	S	L7 AND GLP
L14	4	S	L8 AND GLP
		E	NARASIMHAN CHAKA/ AU
L15	29	S	E6

L16 1 S L15 AND GLP